Aspects of the Palladium-Catalyzed Coupling between Aryl Halides and 2-Amidoacrylates

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The effect of using different salts, bases, catalysts and solvents as well as protecting groups in 2-amidoacrylate derivatives (olefin component) in the Heck coupling with iodobenzene has been studied. Salt effects, resulting in increased yields, were observed in combination with either $NaHCO_3$ or triethylamine as the base. $Pd(OAc)_2$, $PdCl_2$, Pd/C and hydrogen-activated Pd black could all be used as catalyst with similar results. The best solvents were DMF or acetonitrile. Olefins **1a** and **1c**, both carrying orthogonal protecting groups, show the most potential for further applications in peptide synthesis.

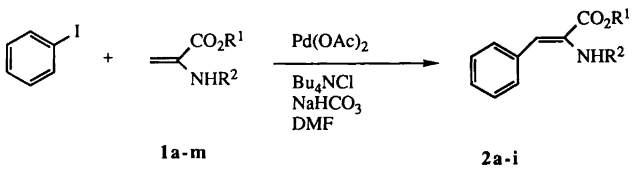
1,2-Diiodobenzene and 1,8-diiodonaphthalene did not give any coupling products and 1-bromo-2-iodobenzene gave only mono-coupling in modest yield. In fact, small amounts of either 1,2-diiodobenzene or 1,8-diiodonaphthalene inhibited the coupling in other, normally reactive, cases. In experiments stoichiometric in $Pd(OAc)_2$, it was found that an indolecarboxylic acid derivative was formed from iodobenzene, 2-bromoiodobenzene and 1,2-diiodobenzene, suggesting that *ortho*-palladation of a phenyl didehydroalanine derivative is involved.

The Heck reaction has been used for the preparation of a vast number of vinylated aromatics or dienes and has been reviewed extensively by Heck and others.[1,2] The original conditions for the reaction, i.e. aryl halide, olefin, Pd/C or a palladium(II) salt in the presence of a tertiary amine and in some cases a phosphine ligand, are not useful for many kinds of olefinic substrates, however. The literature contains a number of reports describing various conditions for the coupling of specific types of olefin.[3] We have previously synthesized didehydroamino acid derivatives by using the Heck reaction (Jeffery conditions) for the coupling of 2-amidoacrylates with iodo aromatics,[4–6] and recently it was reported by Cacchi *et al.* that aryl or vinyl *triflates* can also be used.[7] The didehydroamino acid derivatives formed in these Pd-catalyzed reactions generally have the *Z* configuration, which makes them particularly suitable for asymmetric catalytic hydrogenation.[8] Although we recommended the conditions described by Jeffery, i.e., phase-transfer conditions (Bu_4NCl) in *N,N*-dimethylformamide (DMF) with palladium acetate as catalyst and $NaHCO_3$ as base,[9,10] for the coupling of *2-amidoacrylate derivatives,* little is known about the influence of the different components.

We describe here how some aspects of the nature of the olefin (i.e. the protecting groups of the 2-amidoacrylates), aryl halide, catalyst, base, added salt, and solvent affect the yield of the coupling product. The objective of this study was solely to gain more information on the reaction, and no effort was made to optimize the yields.

Results and discussion

The experiments were all based on the standard reaction conditions given previously (Scheme 1)[4] and varied with respect to the parameters mentioned. Unless stated otherwise iodobenzene was used as the aryl halide component and, in order to increase the accuracy, most experiments were performed twice.



1a-m **2a-i**

Scheme 1.

Olefins. Our efforts to synthesize peptides cross-linked with doubly armed aromatic amino acid residues (**5**),[6] require that all four terminals have different, i.e., orthogonal protecting groups. Thus, in addition to the well behaved **1a**, we needed complementary olefin components. Olefins with *N*-Boc-protection turned out to give similar yields irrespective of the carboxylate protecting group (methyl, ethyl, or benzyl esters),[4,5] and we therefore investigated some methyl 2-amidoacrylates carrying different amino-

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Table 1. Yields in the couplings of olefins **1a–m** and **3** with iodobenzene.[a,b]

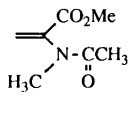
Entry	Olefin	R^1	R^2	Coupling product	Yield[c] (%)
1	**1a**	Bn	Boc	**2a**	80,[d] 79[d]
2	**1b**	Me	CO_2Me	**2b**	64,[d] 38,[d] 41[e]
3	**1c**	Me	TEOC	**2c**	41,[d] 75,[e] 69[e]
4	**1d**	Me	CO_2CH_2-*p*-$NO_2C_6H_4$	**2d**	53,[d] 29[e]
5	**1e**	Me	CO_2CH_2-*p*-$CH_3OC_6H_4$	**2e**	50,[d] 26[e]
6	**1f**	Me	$CO_2CH_2CCl_3$	–	0,[d] 0[e]
7	**1g**	Me	$COCH_2NHZ$	–	0,[d] 0[d]
8	**1h**	Me	$COCH_2NHBoc$	–	0[d]
9	**1i**	Me	Boc	**2f**	71[f]
10	**1j**	Me	COMe	**2g**	73[f]
11	**1k**	Et	Z	**2h**	45[f]
12	**1l**			**2i**	79[f]
13	**1m**			–	0[f]
14	**3**			**4**	33,[d] 19[d]

[a]The reactions were performed in DMF with $Pd(OAc)_2$ as the catalyst, $NaHCO_3$ as the base and Bu_4NCl as the phase-transfer agent using the amounts and conditions described in the Experimental section. [b]Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; TEOC = 2-(trimethylsilyl)ethoxycarbonyl; Z = benzyloxycarbonyl. [c]Yield of isolated products. [d]In the absence of hydroquinone. [e]In the presence of hydroquinone. [f]Ref. 4.

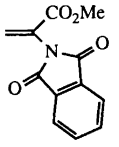
protecting groups (**1b–1h**). The results are summarized in Table 1 (entries 2–8). Olefin **1c**[6] (entry 3) proved to be the best, provided that the reaction was performed in the presence of a trace of hydroquinone to avoid polymerization of the olefin. The other 2-amidoacrylates, **1b**, **1d** and **1e** (entries 2, 4 and 5, respectively) gave lower yields and, in some cases, the addition of a radical scavenger lowered the yield even more. The trichloroethyl protected olefin **1f** (entry 6) was not stable under the coupling conditions and, unfortunately, the dipeptide olefins **1g** and **1h** (entries 7 and 8, respectively) did not react at all. It is possible that these dipeptides coordinate too strongly to palladium by chelation.

A modest yield (ca. 20–30%) of the tetrasubstituted olefin **4** was obtained using (*Z*)-2-amidocrotonate **3** (entry 14), which was synthesized from the appropriately protected threonine derivative. The *Z* configuration of **4** is proposed based on the commonly accepted mechanism of the Heck reaction: a *syn* addition of Ar–Pd–I to the double bond, followed by a *syn* elimination of H–Pd–I. The cinnamate **2a** resisted further coupling with iodobenzene.

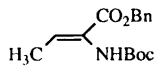
Other olefins have been tested previously.[4] High yields of coupling products were obtained using the Boc-protected olefins **1a** and **1i**, as well as the olefins with *N*-acetyl protection **1j** and **1l** (entries 1, 9, 10 and 12, respectively). *N*-Acetyl protection is, however, not well suited for peptide synthesis. The use of **1k**, containing the benzyloxycarbonyl



1l



1m



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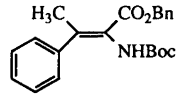

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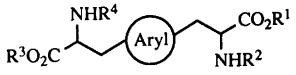

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protecting group, resulted in low yields of coupling product (entry 11) and methyl 2-(phthalimido)acrylate (**1m**) did not participate at all in the reaction (entry 13).

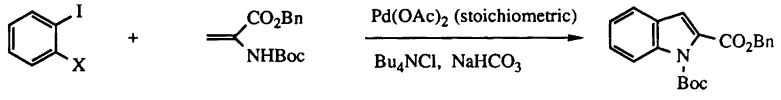
In conclusion, the 2-amidoacrylates **1a** and **1c** are the olefins that best fulfil the requirements of giving good yields in the coupling reaction and carrying orthogonal protecting groups. Thus, hydrogenation of the C=C double bond of the resulting aromatic didehydroamino acid derivatives provides protected amino acids suitable for peptide synthesis.[11]

Aryl halides. We previously showed that a number of iodoaromatics with varying substitution patterns as well as diiodoaromatics and bromo(iodo)aromatics gave either mono-coupling or bis-coupling products.[4–6] Curiously, 1,2-diiodobenzene did not seem to react at all under palladium catalysis although 1,3-diiodo- and 1,4-diiodo-benzene gave fair yields of bis-coupling products.[6]

It was then found that 1,8-diiodonaphthalene gave no coupling product and that the presence of only a small amount of this compound or 1,2-diiodobenzene [3 equivs. compared with $Pd(OAc)_2$] completely suppressed the reaction between iodobenzene and **1a**. Apparently the Pd cata-

lyst reacts faster with 1,2-diiodobenzene and 1,8-diiodonaphthalene than with iodobenzene.

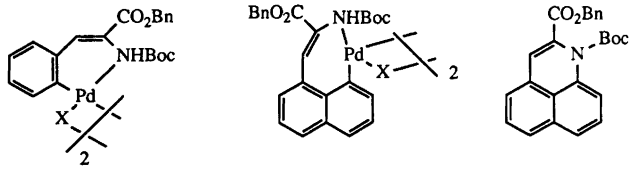
Since Heck *et al.*[12] and de Meijere *et al.*[13] successfully used 1,2-diiodo-, 1,2-dibromo-, or 1-bromo-2-iodo-benzene in bis-couplings with methyl acrylate and styrene, it is likely that the lack of coupling in the cases mentioned is related to the 2-amidoacrylate structure. The formation of an organopalladium intermediate, stable enough to prevent palladium from taking part in the catalytic reaction would then be reasonable. The following experiments support this proposal. First, oxidative addition of Pd(0) [see below for the reduction of Pd(II) to Pd(0)] to 1,2-diiodobenzene and 1,8-diiodonaphthalene seems to take place, since the diiodoarenes were completely consumed in the presence of a stoichiometric amount of $Pd(OAc)_2$. Moreover, the presence of either free iodide ions, or iodide loosely bonded to palladium, e.g., in Ar–Pd–I[14] was indicated by the precipitation of AgI on addition of $AgNO_3$ to reaction mixtures containing 1,2-diiodobenzene, stoichiometric $Pd(OAc)_2$ and $NaHCO_3$ with or without olefin **1a**. No AgI was formed in the absence of the palladium salt.



X = H, I, Br **1a** **6**

Scheme 2.

Secondly, iodobenzene, 1-bromo-2-iodobenzene and 1,2-diiodobenzene all gave the indole-2-carboxylic acid derivative **6** (19–30 %) in the presence of the olefin **1a**, $NaHCO_3$, Bu_4NCl and a stoichiometric amount of Pd $(OAc)_2$ (Scheme 2). The formation of **6** indicates the existence of an *ortho*-palladated complex such as **7**, where the palladium atom is coordinated to either the nitrogen atom or, less likely, to the carbonyl oxygen of the carbamate group. Here we assume that the primary coupling product originating from iodobenzene is *ortho*-palladated by the electrophilic $Pd(OAc)_2$ while those originating from the bis-haloaromatics undergo oxidative addition with Pd(0) in the second step. Both of these reaction types may lead to the Pd(II)-complex **7**. Apparently, the formation of the indole **6** requires an amount of palladium acetate equimolar to the amount of the halobenzene derivative. Thus, palladium would be prevented from acting as a catalyst by being tied up in complex **7**. Attempts to trap **7** with methyl iodide[15] or styrene[16] were unsuccessful.



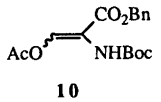
7 **8** **9**

ortho-Palladated complexes stabilized by a nitrogen donor ligand have frequently been described in the literature,[17] and metal-induced ring-closures producing indoles are well known, although when palladium intermediates are involved all described methods refer to aniline derivatives.[18] One procedure utilizing copper(I) catalysis in the presence of sodium hydride, however, makes use of substrates very similar to 2-amidocinnamates as shown in Scheme 3.[19]

In analogy with the above ideas we propose that complex **8** is formed in the experiments where 1,8-diiodonaphthalene is used, although in this case we have not been able to isolate either the expected ring-closure product **9** or the complex **8**. The ring-closure **7** → **6** should obviously be more advantageous than **8** → **9**, since only in the former case is a new aromatic ring formed. Interestingly, compounds similar to **9** have been prepared *via* a palladium complex of 1-iodo-8-dimethylaminonaphthalene.[20]

Although the presence of phosphines is beneficial in coupling reactions with aryl bromides[1,3a,12a] and aryl iodides,[14b,21] the opposite can also be true.[22–24] In our case bromobenzene gave 25 % and iodobenzene gave 80 % **2a** in the absence of phosphine, while the presence of tri(*o*-tolyl)-phosphine gave 42 and 35 %, respectively. Although aroyl chlorides have been used successfully as substrates in similar coupling reactions,[25] benzoyl chloride was unreactive under our standard reaction conditions.

Catalyst. The generally accepted first step in the Heck reaction is an oxidative addition of Pd(0) to the aryl halide,[1] and it has been demonstrated that Pd-atoms oxidatively insert into carbon–halogen bonds of several types of organohalides.[26] Hence, if $Pd(OAc)_2$ or $PdCl_2$ is used as catalyst, Pd(II) must first be reduced to Pd(0). It has been suggested, that this reduction may occur, e.g., *via* addition of palladium acetate to the olefin followed by elimination of PdHOAc.[1] In such a process, the acetoxylated olefin **10**



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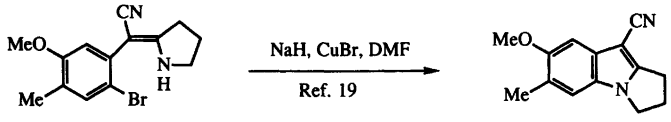

Scheme 3.

would be formed in an amount comparable to the amount of catalyst. However, we did not observe this product in the ^{1}H NMR spectrum of a filtered sample from the mixture containing the olefin **1a**, Bu_4NCl, $NaHCO_3$ and a *stoichiometric* amount of palladium acetate in deuteriated acetonitrile, even after heating at 85 °C for 1 h. The only olefinic signals originated from **1a**.

It is therefore likely that Pd(II) is reduced by some other constituent of the reaction mixture. There are indications in the literature that $Pd(OAc)_2$ can be reduced to Pd(0) by other solvents than alcohols,[27] and indeed, we noticed that $Pd(OAc)_2$ was readily reduced when heated at 85 °C in DMF, DMSO, or acetonitrile. After a few minutes, the mixture became dark and palladium metal began to deposit; after 16 h a palladium mirror had formed in acetonitrile. In addition to the reduction of $Pd(OAc)_2$ by the solvent, it may be reduced by some nitrogenous contaminants remaining from its preparation.[27,28] $PdCl_2$ behaved differently: after 16 h at 85 °C a solution of $PdCl_2$ in DMF showed negligible signs of palladium metal and the solution had become only a darker yellow. However, some Pd(0) could be present in colloidal form, which is difficult to confirm visually since both colloidal Pd(0)[29] and Pd(II)-complexes of amides[30] are reported to be brownish to dark brown.

In any case, Pd(II) can be reduced by various reductants to give catalytically active Pd(0) species. As expected $Pd(OAc)_2$, $PdCl_2$ and Pd/C gave similar yields of coupling products with iodobenzene and 1,4-diiodobenzene. Based on kinetic considerations it has been suggested that the palladium particles should be prevented from agglomeration in order to act as highly effective catalysts.[31] For synthetic purposes, however, we now find that the particles may have a considerable size and still behave as effective catalysts. Thus, the palladium particles obtained from the solvent-washed mirror formed in the reduction of $Pd(OAc)_2$ with acetonitrile, as well as the particles obtained by hydrogen activation (in DMF) of Pd-black worked well as catalysts. In the latter case, small particles were removed by sedimentation followed by removal of the supernatant before the coupling reaction. Surprisingly, when the mixture obtained by heating $Pd(OAc)_2$ in DMF at 85 °C for 18 h under nitrogen (i.e. the usual reaction conditions), and obviously containing palladium particles of various sizes, was used as the catalyst, only traces of **2a** were observed by TLC. No coupling occurred when the catalyst was omitted or if $Ni(acac)_2$ was used in place of the palladium catalyst.

Obviously, effective palladium catalysts are obtained by starting from many different sources of the metal. The initial particle size does not seem critically important since catalytically active particles may be formed *in situ*.

Bases and salts. The presence of a base in the coupling reactions is essential as has already been pointed out by Heck *et al.*,[1] and this was also confirmed in our experiments. Little or no coupling occurred when the base was omitted (entries 1 and 2 in Table 2), while the presence of sodium hydrogencarbonate gave a 60 % yield and triethylamine gave a 50 % yield of **2a** (entries 3 and 11, respectively).

Table 2. Dependence of base, tetrabutylammonium salt and added ions on the coupling between iodobenzene and olefin **1a**.[a]

Entry	Base	Phase-transfer agent	Added salt	Yield of **2a**[b] (%)
1	–	–	–	0, 0
2	–	Bu_4NCl	–	6, 9
3	$NaHCO_3$	–	–	60,59
4	$NaHCO_3$	Bu_4NCl	–	80,79
5	$NaHCO_3$	Bu_4NBr	–	85, 80, 88
6	$NaHCO_3$	Bu_4NI	–	52, 55, 57
7	$NaHCO_3$	Bu_4NCl	NaI	58, 66
8	$NaHCO_3$	Bu_4NF	–	0[e]
9	$NaHCO_3$	Bu_4NHSO_4	–	0[e]
10	$NaHCO_3$	–	LiCl	67, 67
11	Et_3N[c]	–	–	52, 52
12	Et_3N[c]	Bu_4NCl	–	81, 83
13	Et_3N[c]	–	LiCl	76, 72
14	Et_3N[d]	–	–	54, 45
15	Et_3N[d]	Bu_4NCl	–	55, 57

[a]The reactions were performed in DMF with $Pd(OAc)_2$ as the catalyst using the amounts and conditions described in the Experimental section. [b]Yield of isolated product in single, duplicate or triplicate experiments. [c]0.95 mmol (2.4 equiv. relative to iodobenzene). [d]0.38 mmol (1.0 equiv. relative to iodobenzene). [e]No olefin was left after the reaction.

The Jeffery conditions[9] involve the use of a phase-transfer agent, which seems important when the insoluble $NaHCO_3$ is used as a base. In agreement with this the yields were higher when Bu_4NCl and Bu_4NBr were used in combination with $NaHCO_3$ (entries 4 and 5, respectively) than in the absence of these phase-transfer agents under otherwise identical reaction conditions (entry 3). Bu_4NI gave a moderate but significant decrease in yield (entry 6). Iodide binds more strongly to Pd(II) than chloride[32] and it is possible that higher concentrations of iodide ions result in a decreased ability of the $ArPd(L_2)I$ complex (L = e.g. solvent, halide ion) to coordinate to the olefin. Indeed, the addition of 1 equiv. (0.38 mmol) of sodium iodide to a standard reaction mixture containing $NaHCO_3$ and Bu_4NCl caused a decrease in yield (entry 7). Other tetrabutylammonium salts such as Bu_4NF and Bu_4NHSO_4 did not work; the ester functionality of the olefin was hydrolyzed, and no coupling product was formed (entries 8 and 9).

The presence of Bu_4NCl also resulted in a higher yield when Et_3N was the base (entry 12). Here, the phase-transfer effect should not be involved since Et_3N is soluble in DMF in contrast with $NaHCO_3$. Other aspects must then be considered such as ligand and ion effects. Equilibria between several intermediate Pd complexes, carrying different and/or a variable number of ligands, may exist in solution,[33] and it is plausible that these species give the desired products to different degrees. Indeed, ligand and ion effects have been reported. Lithium chloride promotes

palladium-catalyzed cross-couplings between aryl and vinyl triflates and organostannanes,[34] and different lithium halogenides have been shown to influence the regiochemistry in the arylation of enol ethers using aryl triflates as arylating agents.[35] Moreover, in the reactions of vinyl and aryl triflates with methyl 2-acetamidoacrylate, the presence of lithium chloride in some cases resulted in higher yields.[7] All these cases involve triflates, and the chloride ions are thought to exchange with the triflate ions in the oxidative addition complexes Ar–Pd–OTf to produce the more reactive Ar–Pd–Cl complexes. In a recent communication it was shown that chloride ions were also beneficial for the coupling of aryl iodides with methyl 2-acetamidoacrylate using Pd/C as the catalyst and K_2CO_3 as base.[36] Such a specific chloride-ion effect remains obscure, however, since we found that both Bu_4NCl and Bu_4NBr worked equally well when $NaHCO_3$ was the base (entries 4 and 5). When Bu_4NCl was replaced with LiCl the yields of the coupling product decreased somewhat (entries 4, 10, 12 and 13), but were still higher than in experiments without added salts.

It has been suggested that triethylamine coordination may stabilize the oxidative addition product PhPdI.[23] In the example cited, where allylic alcohols were used as substrates, this stabilization was advantageous for the reaction. In our case, however, the amine coordination may, instead, lower the reactivity owing to the steric demands of the 2-amidoacrylate. The presence of chloride ions may break such undesirable coordination, thus explaining the chloride-ion effect, which was noticed in experiments where an excess of triethylamine was used (2.4 equiv. compared with iodobenzene). Curiously, an equimolar amount of the same base gave 45–55 % of **2a** whether Bu_4NCl was present or not (entries 14 and 15).

We may conclude that, depending on the base used in this coupling reaction, there are different effects of added salts; with insoluble bases such as $NaHCO_3$, the phase-transfer effect may be important, but with soluble and presumably rather strongly metal-coordinating bases such as amines, the halide ion may compete with the amine to give a more reactive complex. Salts containing fluoride and hydrogensulfate ions seems incompatible with the olefin component used in this investigation.

Solvents. As shown in Table 3 the yield is highly dependent on the solvent used. The solvents tested were selected from all areas of the solvent descriptor space as defined by Carlson *et al.*[37] To some extent the large variation in yields reflects the ability of the solvents to coordinate to palladium.[38] Various formamide derivatives form coordination complexes with palladium(II),[30,39] and, indeed, coordinating solvents such as DMF (entry 1) and acetonitrile (entry 8) gave high yields (ca. 80 %), in contrast with the weak coordinators toluene (52 %, entry 7) and heptane (22 and 48 %, entry 9).

The increasing bulkiness in DMF < *N,N*-diethylformamide < *N,N*-diisopropylformamide is accompanied by decreasing yields (entries 1, 2 and 3, respectively), indicating

Table 3. Dependence of solvent on the coupling between iodobenzene and olefin **1a**.[a]

Entry	Solvent	Yield of coupling product **2a**[b] (%)
1	*N,N*-Dimethylformamide	80, 79
2	*N,N*-Diethylformamide	65, 60
3	*N,N*-Diisopropylformamide	10, 19
4	*N*-Methylformamide	40, 47
5	Formamide	0, 0[c]
6	Dimethyl sulfoxide	37, 48
7	Toluene	52, 52
8	Acetonitrile	73, 84
9	Heptane	22, 48

[a]The reactions were performed with $Pd(OAc)_2$ as the catalyst, $NaHCO_3$ as the base and Bu_4NCl as the phase-transfer agent using the amounts and conditions described in the Experimental section. [b]Yield of isolated product in duplicate experiments. [c]No olefin was left after the reaction.

that solvent coordination and steric factors are involved. It could, however, be ruled out that increased bulkiness makes the solvent coordinate so weakly to palladium that palladium metal precipitates before participating in the reaction. In fact such a precipitate was formed faster with DMF and *N,N*-diethylformamide than with *N,N*-diisopropylformamide. The formation of palladium metal does not necessarily mean that the catalytic action is blocked as mentioned. The decrease in yield when the bulkiness of the solvent was increased is better explained by steric crowding in the palladium(II) complex obtained after the oxidative addition to iodobenzene, which makes the *syn*-addition to the olefin more difficult. However, steric hindrance obviously cannot explain the low yield obtained when *N*-methylformamide was the solvent (entry 4), and here some other reason must be found. In formamide (entry 5), the olefin is consumed after 16 h at 85 °C, possibly through a nucleophilic addition of the solvent to the olefin by analogy with the behaviour of various amines.[40] Such addition may also, to some extent, take place with *N*-methylformamide.

Dimethyl sulfoxide may coordinate to palladium with either the sulfur atom or the oxygen atom, although coordination through sulfur predominates, at least when steric crowding is not involved.[39] The possibility of DMSO to act as a strongly binding ligand to palladium could make the catalyst less reactive, thus explaining the modest yield when this solvent is used (entry 6). Furthermore, small amounts of dimethyl sulfide may be present, either as a contaminant in the solvent or through deoxygenation of palladium-coordinated sulfoxide.[41] Dimethyl sulfide may act as a catalyst poison by forming strong complexes with palladium.[42]

The irreproducibility of the yields when the reaction was performed in heptane (entry 9) is probably due to several factors such as the low solubility of the base and also to the lack of coordinating ability of this apolar solvent.

Conclusions

The palladium-catalyzed reaction between aryl halides and 2-amidoacrylates proceeds smoothly when the Jeffery[9] conditions, or slight modifications thereof, are applied. Both sodium hydrogencarbonate and triethylamine may be used as bases. Hitherto the best results have been obtained when sodium hydrogencarbonate was the base in combination with tetrabutylammonium chloride or tetrabutylammonium bromide as phase-transfer agents. A yield-increasing salt effect was also noticed when triethylamine was the base. Of the olefins tested, **1a** and **1c** are the two most useful candidates for further applications towards peptide synthesis. The best solvents are DMF or acetonitrile and any of $Pd(OAc)_2$, $PdCl_2$, Pd/C and hydrogen activated Pd black may be used as catalyst. The apparent contradictory results that the reaction works well in DMF but that Pd particles generated in DMF are not catalytically active are intriguing. However more sophisticated experiments are necessary to reveal the nature of the actual catalyst, be it atomic Pd, Pd complexes, Pd clusters or even larger particles.

Experimental

NMR spectra were recorded with a Varian XL-300 spectrometer. The high resolution mass spectrum was recorded on a JEOL SX102 spectrometer. Melting points (uncorrected) were determined with a Reichert microscope. Thin-layer chromatography (TLC) was performed on Merck precoated silica gel F-254 plates and spots were visualized with UV light. 1,8-Diiodonaphthalene,[43] benzyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (**1a**),[4] and methyl 2-{2-[(trimethylsilyl)ethoxycarbonyl]amino}acrylate (**1c**)[6] were prepared by literature procedures. The 2-amidoacrylates **1b**, **1d**, **1e**, **1f**, **1g**, and **1h** were prepared from the appropriately protected serine derivatives by an elimination process described in an earlier publication,[4] and has physical data as shown below. The couplings with olefins **1a**, **1i**, **1j**, **1k**, **1l**, and **1m**, as well as data for the 2-amidocinnamates **2a**, **2f**, **2g**, **2h**, and **2i**, have been described in more detail previously.[4] The multiplicities in the NMR data refer to the appearance of the actual spectra and not to theoretical analyses.

Methyl 2-[(methoxycarbonyl)amino]acrylate (**1b**). Yield after chromatography (heptane–EtOAc 7:1): 72 %, m.p. 45–47 °C (EtOAc–petroleum ether). Anal. $C_6H_9NO_4$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (3 H, s, CO_2CH_3), 3.84 (3 H, s, CO_2CH_3), 5.77 (1 H, d, *J* 1.5 Hz, HC=), 6.23 (1 H, s, HC=), 7.18 (1 H, br s, NH).

Methyl 2-[(p-nitrobenzyloxycarbonyl)amino]acrylate (**1d**). Yield after chromatography (heptane–EtOAc 5:1): 77 %, m.p. 94–95 °C (EtOAc–hexane). Anal. $C_{12}H_{12}N_2O_6$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (3 H, s, CO_2CH_3), 5.26 (2 H, s, PhCH_2), 5.82 (1 H, m, HC=), 6.24 (1 H, s, HC=), 7.32 (1 H, br s, NH), 7.54, 8.23 (4 H, AA'BB' with further couplings, J_{AB} 8.9 Hz, ArH).

Methyl 2-[(p-methoxybenzyloxycarbonyl)amino]acrylate (**1e**). Yield after chromatography (heptane–EtOAc 5:1): 80 %, m.p. 76–79 °C (EtOAc–petroleum ether). Anal. $C_{13}H_{15}NO_5$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 5.10 (2 H, s, PhCH_2), 5.78 (1 H, d, *J* 1.5 Hz, HC=), 6.24 (1 H, s, HC=), 6.90, 7.33 (4 H, AA'BB' with further couplings, J_{AB} 8.8 Hz, ArH), 7.21 (1 H, br s, NH).

Methyl 2-[(2,2,2-trichloroethoxycarbonyl)amino]acrylate (**1f**). Yield after chromatography (heptane–EtOAc 10:1): 29 % from serine methyl ester hydrochloride, oil. Anal. $C_7H_8Cl_3NO_4$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (3 H, s, CO_2CH_3), 4.78 (2 H, s, CH_2CCl_3), 5.87 (1 H, m, HC=), 6.27 (1 H, s, HC=), 7.43 (1 H, br s, NH).

Z-Gly-Δ-Ala-OMe (**1g**). Yield after chromatography (heptane–EtOAc 1:1): 69 %, m.p. 71–74 °C (EtOAc–petroleum ether). Anal. $C_{14}H_{16}N_2O_5$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (3 H, s, CO_2CH_3), 3.97 (2 H, d, *J* 5.9 Hz, CH_2), 5.16 (2 H, s, PhCH_2), 5.42 (1 H, br s, NH), 5.93 (1H, d, *J* 1.4 Hz, HC=), 6.60 (1 H, s, HC=), 7.36 (5 H, m, ArH), 8.19 (1 H, br s, NH).

Boc-Gly-Δ-Ala-OMe (**1h**). Yield after chromatography (heptane–EtOAc 1:1): 88 %, oil. Anal. $C_{11}H_{18}N_2O_5$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 [9 H, s, $C(CH_3)_3$], 3.84 (3 H, s, CO_2CH_3), 3.88 (2 H, d, *J* 6.0 Hz, CH_2), 5.17 (1 H, br s, NH), 5.91 (1 H, d, *J* 1.4 Hz, HC=), 6.60 (1 H, s, HC=), 8.31 (1 H, br s, NH).

Benzyl 2-[(tert-butoxycarbonyl)amino]crotonate (**3**) was prepared by a modification of a published procedure.[44] Methanesulfonyl chloride (1.5 g, 13 mmol) in dry pyridine (3 ml) was added to a solution of *N*-Boc-DL-threonine benzyl ester (2.0 g, 6.5 mmol) in dry pyridine (20 ml) at −20 °C. After being stirred at this temperature for 1 h, the mixture was kept in the refrigerator overnight, and was finally poured into water. The solution was extracted with CH_2Cl_2 and the combined organic phase was washed with water, dried (Na_2SO_4) and concentrated by evaporation. The last traces of pyridine were removed by co-evaporation with toluene. The crude mesylate (2.4 g) was dissolved in EtOAc (25 ml) and 1,4-diazobicyclo[2.2.2]octane (Dabco, 1.4 g, 12 mmol) was added. The reaction was complete after 2 h of stirring at room temperature. Water was added and the phases were separated. The organic phase was washed with water, dried (Na_2SO_4), and concentrated by evaporation with a trace of hydroquinone present to avoid radical polymerization. The crude product was chromatographed (heptane–EtOAc 7.5:1) to give 1.5 g (5.2 mmol, 79 %) of **3**, m.p. 83–84 °C (EtOAc–hexane). Anal.

$C_{16}H_{21}NO_4$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 [9 H, s, $C(CH_3)_3$], 1.81 (3 H, d, *J* 7.3 Hz, CH_3), 5.20 (2 H, s, $PhCH_2$), 5.98 (1 H, br s, NH), 6.73 (1 H, q, *J* 7.2 Hz, HC=), 7.36 (5 H, m, ArH).

The *Z* configuration of the product was established by comparison of ^{1}H NMR data with those of a similar compound.[45] The shifts for the β-methyl protons and the vinyl proton for methyl 2-[(*tert*-butoxycarbonyl)amino]crotonate were 1.81 and 6.67 ppm, respectively, for the *Z* form, and 2.05 and 6.78 ppm, respectively, for the *E* form.

Standard procedure for the coupling reaction between iodobenzene and 2-amidoacrylates (**1**). A mixture of iodobenzene (78 mg, 0.38 mmol), 2-amidoacrylate **1** or **3** (0.54 mmol, see Table 1), Pd catalyst (0.011 mmol), base (0.95 mmol of $NaHCO_3$, 0.95 mmol or 0.38 mmol of Et_3N, see Table 2), salt (tetrabutylammonium salt, KCl, LiI or NaI 0.38 mmol, see Table 2) in a solvent (5 ml, see Table 3) was stirred under a nitrogen atmosphere in a screw-cap sealed tube at 85 °C for 16 h. After being cooled, the mixture was diluted with water (25 ml) and extracted with CH_2Cl_2 (3×15 ml). The combined organic phase was washed with water (2×15 ml), dried (Na_2SO_4), and the solvent was evaporated. The products (**2** and **4**) were isolated by chromatography using the eluents given below.

Methyl 2-[(methoxycarbonyl)amino]cinnamate (**2b**). Yield after chromatography (heptane–EtOAc 2.5:1): see Table 1, m.p. 87–92 °C (EtOAc–petroleum ether). Anal. $C_{12}H_{13}NO_4$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (3 H, s, CO_2CH_3), 3.86 (3 H, s, CO_2CH_3), 6.26 (1 H, br s, NH), 7.38 (4 H, m, ArH, HC=), 7.52 (2 H, m, ArH).

Methyl 2-{[2-(trimethylsilyl)ethoxycarbonyl]amino}cinnamate (**2c**). Yield after chromatography (heptane–EtOAc 6:1): see Table 1, m.p. 58–63 °C (EtOAc–petroleum ether). Anal. $C_{16}H_{23}NO_4Si$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.020 [9 H, s, $Si(CH_3)_3$], 0.93 (2 H, m, CH_2Si), 3.86 (3 H, s, CO_2CH_3), 4.16 (2 H, t, *J* 8.5 Hz, CH_2CH_2Si), 6.21 (1 H, br s, NH), 7.31 (1 H, s, HC=), 7.36 (3 H, m, ArH), 7.53 (2 H, dd, *J* 7.9, 1.5 Hz, ArH).

*Methyl 2-[*p*-nitrobenzyloxycarbonyl)amino]cinnamate* (**2d**). Yield after chromatography (heptane–EtOAc 3:1): see Table 1, m.p. 93–96 °C (EtOAc–petroleum ether). Anal. $C_{18}H_{16}N_2O_6$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (3 H, s, CO_2CH_3), 5.19 (2 H, s, $ArCH_2$), 6.42 (1 H, br s, NH), 7.34 (5 H, m, ArH), 7.40 (1 H, s, HC=), 7.52, 8.18 (4 H, AA'BB' with further couplings, J_{AB} 8.3 Hz, ArH).

*Methyl 2-[(*p*-methoxybenzyloxycarbonyl)amino]cinnamate* (**2e**). Yield after chromatography (heptane–EtOAc 2.5:1): see Table 1, m.p. 78–79 °C (EtOAc–petroleum ether). Anal. $C_{19}H_{19}NO_5$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (6 H, s, CO_2CH_3 and OCH_3), 5.05 (2 H, s, $ArCH_2$), 6.30 (1 H, br s, NH), 6.87 (2 H, d, *J* 8.3 Hz, ArH), 7.24 (1 H, s, HC=), 7.35 (5 H, m, ArH), 7.50 (2 H, m, ArH).

*Benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-methylcinnamate* (**4**). Yield after chromatography (heptane–EtOAc 6:1): see Table 1, m.p. 125–127 °C (EtOAc–petroleum ether). Anal. $C_{22}H_{25}NO_4$: C, H, N. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 [9 H, s, $C(CH_3)_3$], 2.12 (3 H, s, CH_3), 4.91 (2 H, s, $PhCH_2$), 6.07 (1 H, br s, NH), 6.90 (2 H, m, ArH), 7.14–7.25 (8 H, m, ArH).

Benzyl N-*[*tert*-butoxycarbonyl)indole-2-carboxylate* (**6**). *(a) From 1,2-diiodobenzene.* A mixture of 1,2-diiodobenzene (63 mg, 0.19 mmol), **1a** (63 mg, 0.23 mmol), Pd $(OAc)_2$ (43 mg, 0.19 mmol), Bu_4NCl (112 mg, 0.38 mmol) and $NaHCO_3$ (80 mg, 0.95 mmol) in DMF (5 ml) was stirred at 85 °C for 16 h. After standard work-up (see above), the crude product was chromatographed on silica gel (heptane–EtOAc 15:1) to yield 25 mg of a mixture of **6** and **1a**. These two compounds have the same R_f-value on silica gel in all of the eluents tested, but were readily separated on a reversed-phase C-18 column using methanol–water 7:1 as the eluent to give 20 mg (0.057 mmol, 30 %) of **6**.

(b) From iodobenzene. A mixture of iodobenzene (390 mg, 1.9 mmol), **1a** (630 mg, 2.3 mmol), $Pd(OAc)_2$ (430 mg, 1.9 mmol), Bu_4NCl (560 mg, 1.9 mmol) and $NaHCO_3$ (400 mg, 4.8 mmol) in DMF (50 ml) was stirred at 85 °C for 16 h. After standard work-up (see above), the crude product was chromatographed on silica gel (heptane–EtOAc 15:1) to yield 130 mg (0.37 mmol, 19 %) of **6** (**1a** was, in this reaction, completely consumed).

Data for **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 [9 H, s, $C(CH_3)_3$], 5.36 (2 H, s, $PhCH_2$), 7.15 (1 H, s, ArH), 7.25–7.46 (7 H, m, ArH), 7.59 (1 H, dd, *J* 7.9, 0.7 Hz, ArH), 8.08 (1 H, d, *J* 8.5 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ 27.8 [$C(CH_3)_3$], 67.1 (Ph–CH_2), 84.7 [$C(CH_3)_3$], 114.9, 115.3, 122.2, 123.3, 126.9, 127.5, 128.3, 128.4, 128.6, 130.4, 135.6, 138.0 (aromatic C and CH), 149.3 (C=O carbamate), 161.6 (C=O ester). MS (EI, 30 eV): M^+, Found: 351.1480. Calc. for $C_{21}H_{21}NO_4$: 351.1470.

Further proof for the structure of **6** was obtained by treating a solution of **6** (105 mg) in CH_2Cl_2 (8 ml) with trifluoroacetic acid (6 ml) during 30 min at room temperature. Evaporation, followed by hydrogenolysis in ethanol with 10 % Pd/C as catalyst for 2 h, gave, after chromatography (SiO_2, heptane–EtOAc–methanol 1:1:0.1), a product that was identical with a commercial sample of indole-2-carboxylic acid according to the ^{1}H NMR spectrum and TLC R_f value (0.4 in heptane–EtOAc–methanol 1:1:1).

Attempted trapping of complex **7** *with methyl iodide.* A mixture of 1,2-diiodobenzene (63 mg, 0.19 mmol), **1a** (147 mg, 0.53 mmol), $Pd(OAc)_2$ (43 mg, 0.19 mmol), Bu_4NCl (112 mg, 0.38 mmol) and $NaHCO_3$ (80 mg, 0.95 mmol) in DMF (5 ml) was stirred at 85 °C for 20 h. After cooling, methyl iodide (405 mg, 2.85 mmol) was added and the mixture was stirred for 4 h at 50 °C, and then for 16 h at 85 °C. TLC analysis, using an authentic sample of 2-{2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl}

toluene[6] as a reference, showed that this compound was not formed.

Attempted trapping of complex **7** *with styrene. (a) From 1,2-diiodobenzene.* A mixture of 1,2-diiodobenzene (63 mg, 0.19 mmol), **1a** (147 mg, 0.53 mmol), $Pd(OAc)_2$ (43 mg, 0.19 mmol), Bu_4NCl (112 mg, 0.38 mmol) and $NaHCO_3$ (80 mg, 0.95 mmol) in DMF (5 ml) was stirred at 85 °C for 20 h. After cooling, styrene (40 mg, 0.38 mmol) was added and the mixture was stirred for 20 h at 85 °C, and then for 3 days at room temperature. TLC analysis showed no spot that could represent 1-{2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl}-2-(2-phenylethenyl)-benzene.

*(b) From 1-{2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)aminoethenyl}-2-bromobenzene.* A mixture of 1-{2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]-ethenyl}-2-bromobenzene[6] (50 mg, 0.12 mmol), styrene (19 mg, 0.18 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol), Bu_4NCl (53 mg, 0.18 mmol) and $NaHCO_3$ (45 mg, 0.54 mmol) in DMF (4 ml) was stirred at 85 °C for 16 h. TLC analysis showed no spot that could represent 1-{2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]-ethenyl}-2-(2-phenylethenyl)benzene.

Inhibition of the coupling between iodobenzene and **1a** *by 1,8-diiodonaphthalene or 1,2-diiodobenzene.* A standard mixture of iodobenzene, **1a** $Pd(OAc)_2$, Bu_4NCl and $NaHCO_3$ in DMF containing 1,8-diiodonaphthalene (4.4 mg, 0.012 mmol or 12.5 mg, 0.033 mmol) was kept at 85 °C for 16 h. When 0.012 mmol [an equimolar amount to Pd $(OAc)_2$] of 1,8-diiodonaphthalene was used, 35 % of **2a** was isolated. With the larger amount of 1,8-diiodonaphthalene, no formation of **2a** was observed according to TLC analysis. Similar results were obtained when 1,8-diiodonaphthalene was replaced with 1,2-diiodobenzene.

Preparation of various Pd(0) catalysts. (a) Activated Pd black. Pd black (5 mg) was hydrogenated at ambient pressure and temperature in DMF (3 ml) for 1 h. Small particles were removed by decantation of the solvent under nitrogen. The hydrogenation procedure was repeated twice, and the remaining particles were used as the catalyst in a coupling experiment between iodobenzene and **1a** according to the standard procedure. The yield of purified **2a** was 86 %. When unactivated particles were used no coupling occurred.

(b) Pd 'mirror'. A solution of $Pd(OAc)_2$ (5 mg) in CH_3CN (2 ml) was kept in a sealed tube at 85 °C for 18 h. The solvent was removed and the palladium mirror that had formed on the walls was rinsed several times under nitrogen with DMF, and was then suspended in DMF. The suspension was used at the catalyst in a coupling reaction between iodobenzene and **1a** according to the standard procedure. The yield of purified **2a** was 75 %. TLC showed that a slightly lower yield was obtained using a palladium mirror that had been kept for several months in CH_3CN (the yield of **2a** was, in this case, estimated to ca. 50 % based on our experience of cases where the magnitude of the TLC spots were compared with isolated yields).

(c) Pd(0) prepared in DMF. A solution of $Pd(OAc)_2$ (5 mg) in DMF (2 ml) was kept in a sealed tube at 85 °C for 18 h. The solvent was removed and the precipitate of black particles was rinsed several times under nitrogen with DMF, and was then suspended in the same solvent. The suspension was used as the catalyst in a coupling reaction between iodobenzene and **1a** according to the standard procedure. The yield of **2a** was estimated to be < 5 %. A similar yield was obtained using the colloidal-looking suspension formed when the reduction of $Pd(OAc)_2$ in DMF was performed with magnetic stirring.

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